REMARKS

Claims 1, 5, 9, 20, 31, and 32, as herein amended, claims 2, 6, 12, 14, 16, 23, 25, 27, 45 and 46, as previously presented, and claims 4, 8, 17, 18, 28 and 29 as filed are pending in the application. Claims 13, 15, 24, 26, 35-44 were cancelled previously, and claims 47 and 48 are cancelled herein without prejudice or disclaimer. Claims 3, 7, 10, 11, 19, 21, 22, 30, 33, 34, 49 and 50 are withdrawn as being directed to a non-elected invention. Should the Examiner require it, Applicant asks that he cancel these claims by Examiner's amendment in order to expedite prosecution of the remaining claims to allowance.

The amendments are fully supported by the specification as filed and no new matter is introduced into the application by way of these amendments. The grounds of rejection contained in the outstanding Office Action have been overcome in part by amendment and traversed in part by Applicants' argument herein.

The claims as amended are enabled by Applicants' specification.

The pending claims stand rejected under 35 U.S.C. §112, first paragraph as being non-enabled. Applicants in response to the previous Action amended the claims to recite neoplastic disease (not all diseases) in humans (not all animals), and further limited the diseases to those associated with the expression or overexpression of one or more RNA species. The claims were further limited to detecting one or more RNA species (or cDNA prepared therefrom) that are associated with a neoplastic disease. The claims were further limited to those RNA species associated with neoplastic disease that are overexpressed with reference to a human population without neoplastic disease. Finally, the bodily fluid assayed according to the amended claims was the acellular fraction of blood, such as blood plasma and serum.

The pending Action continues to assert that the claim, even as amended, are not enabled. The Action states that the limitations recited in claims 1 and 5 read on detected concentrations of said one or plurality of RNA species that are quantitatively the same as those found in the representative population. Without acquiescing to the correctness of this assertion in the Action, Applicants have amended claims 1 and 5 to recite the limitation "when the amplified product or signal of one or more RNA expressed or overexpressed in said neoplastic disease, or cDNA therefrom, is detected in an amount or concentration *greater than* a reference amount or

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concentration for said RNA or cDNA therefrom determined from plasma or serum from a human group or population *without* said neoplastic disease (*emphasis added*). Applicants respectfully contend that this eliminates from the claim the scope objected-to in the Action, as the relevant reference population is individuals without neoplastic disease, and the amount of one or a plurality of RNA species characteristic of neoplastic disease found in the assayed sample is greater than the amount found in the reference population. It will be understood that this amount is not intended to be defined in all instances quantitatively; there will be some cases where expression of any detectable amount of an RNA species is characteristic of neoplastic disease, and said expression is not detectable in a reference population of patients without neoplastic disease. Applicants respectfully contend that these amendments address the concerns raised in the Action regarding the scope of the pending claims in this point.

The Action also states correctly that total extracellular RNA in blood plasma or serum is a complex mixture of many different RNA species, and questions how the relative amount of any particular species can be used by the claimed methods. Applicants respond that the selection of the species to be used will be understood by the skilled worker to be one or a plurality of species that are know to be associated with a neoplastic disease. Also, the entire scope of total extracellular RNA is not amplified using the claimed methods, but only those species that are amplified using primers *specific for* the interrogated species. Specific amplification of a particular RNA or cDNA species, or same multiplex or sequential interrogation of a mixture of RNA species is known in the art, and is know to be achieved through the use of specific primers. Applicants are not claiming specific amplification of a particular RNA or cDNA species *per se*, only methods using said sequence-specific amplification in their inventive methods. Third, claims 31 and 32 are particularly recited as being non-enabled because of an asserted lack of correlation between housekeeping gene expression and cancer. Applicants respectfully contend that this is the point: expression of one or a plurality of RNA species known to be associated with cancer is compared in the same sample with expression of a housekeeping gene, that is not (and is not known to be) associated with cancer. This provides a control for comparison with a reference population, wherein what is compared is the relative ratios of the cancer-associated gene(s) and the housekeeping genes, so that trivial differences in sample preparation, handling and the like do not confound the result obtained.

Applicants respectfully contend that they were the first to provide evidence that human

extracellular disease-associated RNA could be amplified from blood in humans with neoplastic disease, and thus are entitled to the claimed scope since the skilled worker would not have to exercise undue experimentation in view of the disclosure.

Applicant respectfully contends that, having clarified the language recited in the pending claims with his amendment, he has traversed the asserted rejection on lack-of-enablement grounds. Applicant respectfully requests that the Examiner withdraw these grounds of rejection.

The claims as amended are not indefinite.

Claim 9 remains rejected under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Action asks Applicants to clarify how a neoplastic disease can be detected, inferred or monitored using one or a plurality of RNA species.

Applicant notes that Claim 9 as amended recites:

> A method to detect, infer, or monitor a neoplastic disease in a human, wherein the neoplastic disease is associated with the expression or overexpression of one or more tumor-associated human RNA species, the method comprising the steps of determining an amount or concentration or comparative value of one or a plurality of tumor associated human RNA species associated with said neoplastic disease in a portion of plasma or serum from the human, and comparing the amount or concentration or comparative value of one or a plurality of tumor associated human RNA species from plasma or serum of said human to a reference range RNA amount, concentration, or value determined from a defined human group or population without neoplastic disease, wherein a neoplastic disease is detected, inferred, or monitored in a human when the amount or concentration or comparative value of one or a plurality of said tumor-associated human RNA in said human is greater than a defined reference range RNA amount, concentration, or value for said tumor-associated RNA determined from plasma or serum from a human group or population without a neoplastic disease.

Applicants respectfully contend that, as written, the claim recites that the neoplastic disease in a human is detected, inferred or monitored when the amount, concentration or comparative value of one or more of the RNA species assayed is *greater* in the putative patient sample than it is in a reference sample of individuals without neoplastic disease. Applicants respectfully contend that the skilled worker would appreciate these limitations in the claims and that their claims are not indefinite. Applicants respectfully ask that the Examiner withdraw this ground of rejection.

Applicant respectfully contends that, having clarified the language recited in the pending claims with his amendment, he has traversed the asserted rejection on indefiniteness grounds. Applicant respectfully requests that the Examiner withdraw these grounds of rejection.

Applicants file a terminal disclaimer herein to overcome the obviousness-type double patenting rejection.

Applicants acknowledge rejection of the pending claims under the judicially-created doctrine of obviousness-type double patenting over co-owned U.S. Patent Nos. 6,329,179, 6,759,217 and 6,916,634. Applicant files herewith a Terminal Disclaimer to overcome this ground of rejection.

CONCLUSIONS

Applicant believes that all grounds of rejection have been overcome by amendment, and request that the pending claims be passed to issue.

If Examiner Lu believes it to be helpful, he is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
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